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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/809,524	03/15/2001	David E. Lowery	28341/6114.N	4519

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MARSHALL, GERSTEIN & BORUN
6300 SEARS TOWER
233 SOUTH WACKER
CHICAGO, IL 60606-6357

EXAMINER
NAVARRO, ALBERT MARK

ART UNIT	PAPER NUMBER
1645	15

DATE MAILED: 04/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/809,524	Lowery et al
Examiner	**Art Unit**
Mark Navarro	1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above, claim(s) *15-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5, 8, and 10-14* is/are rejected.

7)☒ Claim(s) *6, 7, and 9* is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some* c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restriction

Applicant's are again traversing the restriction requirement of a particular gene being inactivated. Applicant's are asserting that the claims require mutations in at least two genes, and that restriction to a single gene is inconsistent with the claimed invention.

First, Applicant's have not been restricted to a single sequence as argued. Claim one has been examined in its entirety, (any two genes inactivated). The requirement is imposed so that the elected Sequence (SEQ ID No: 1), must be **one** of the **multiple** genes inactivated when a particular gene is to be inactivated. For instance, deleting SEQ ID NO: 1 and 2, or SEQ ID NO: 1 and 3, or SEQ ID NO: 1 and 3 and 4, etc. will be considered. Alternatively, claims in which SEQ ID NO: 2 and 3 are inactivated are withdrawn from further consideration as being drawn to a non-elected invention, (e.g., does not involve inactivation of SEQ ID NO: 1). In other words any claim that requires a generic inactivation or the inactivation of SEQ ID NO: 1 is under consideration. Claim 5 has been examined to the extent that at least SEQ ID NO: 1 has been inactivated.

MPEP 803.04 sets forth that polynucleotides encoding different proteins are separate inventions. The fact that SEQ ID NO: 1 and 2 each encode a protein with a different primary, secondary, and tertiary structure makes them different inventions.

For these reasons the restriction requirement is deemed to be proper and is adhered to.

Claim Rejections - 35 USC § 112

1. Claims 1-4, 8, and 11-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a vaccine composition comprising an immunologically protective amount of an attenuated non-reverting mutant Salmonella bacterium in which ssaT, ssaJ or ssaC are partially deleted, does not reasonably provide enablement for a vaccine composition comprising an immunologically protective amount of an attenuated non-reverting mutant Salmonella bacterium in which two or more genes within the SPI2 region have been inactivated is maintained. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant's are asserting that while Linde reports that some Salmonella strains containing two or more attenuating mutations, which do not involve mutations in at least two SPI2 genes as recited in the pending claims, may be over-attenuated for less susceptible host species, does not mean inoperable. Applicant's assert that whether a given vaccine composition produces a protective immune response after one or twenty inoculations, for example, is irrelevant to the patentability of that vaccine composition. Applicant's further assert that Hensel et al refers to plural strains having single mutations with wild-type levels of replication. Applicant's further

assert that the specification discloses working examples of two species of Salmonella in which two different SPI2 genes (ssaC and ssaT) were inactivated and afforded protection.

Applicant's arguments have been fully considered but are not found to be fully persuasive.

Applicant's arguments are not found to be fully persuasive in view of the teachings of Linde et al and Hensel et al.

Applicant's assert that while Linde reports that some Salmonella strains containing two or more attenuating mutations, which do not involve mutations in at least two SPI2 genes as recited in the pending claims, may be over-attenuated for less susceptible host species, does not mean inoperable. However, Linde et al report that "the protective values after experimental challenge (Table 1) showed that the good results obtained in mice are only in part valid for domestic animals." (See front page). Consequently, in view of the lack of correlation between results obtained in mice and results obtained in domestic animals, one of skill in the art would be forced into undue experimentation to practice the broadly claimed invention.

Applicant's further assert that Hensel et al refers to plural strains having single mutations with wild-type levels of replication. This point is not disputed. However, the question remains since a mutation in ssaC had a wild type level of replication, and a mutation in ssrA had a wild type level of replication, would a double mutation of both ssaC and ssrA also have a wild type level or replication? The answer to this question can only be attained with additional experimentation. This point is further reinforced by the conclusion of Hensel et al that "our

results cast doubt on the conclusion that SPI2 is required for survival of Salmonella in macrophages." (See page 164). Hensel et al further set forth that "Further work on the type III secretion system of SPI2 is required to clarify its role in Salmonella pathogenicity." (See again page 164). It is this further work which must be undertaken by those of skill in the art to elucidate which regions of SPI2 can be inactivated and yet still elicit a protective immune response. Without such guidance, one of skill in the art would be forced into undue experimentation.

Finally, Applicant's assert that the specification discloses working examples of two species of Salmonella in which two different SPI2 genes (ssaC and ssaT) were inactivated and afforded protection. However, Applicant's will note that this rejection has not been applied to any claim which recites an inactivation of ssaC and ssaT. Claims which recite this combination of inactivations are deemed to be fully enabled. However, for the reasons set forth above inactivation of any genes within the SPI2 region, while still displaying the ability to achieve immunoprotection, require excessive experimentation by those of skill in the art.

The claims are drawn to vaccine compositions comprising an immunologically protective amount of a first attenuated, non-reverting mutant Salmonella bacterium in which two or more genes within the SPI2 region have been inactivated.

Linde et al (Vaccine Vol. 8, pp 278-282, 1990) set forth that the use of double or multiple gene disruptions is unpredictable in its effect on virulence and immunogenicity, the introduction of multiple mutations may over attenuate a bacteria for a particular host. (See abstract).

Hensel et al (Molecular Microbiology Vol. 24, pp 155-167, 1997) set forth that Salmonella strains carrying SPI2 mutations in ssaC and ssrA have wild-type levels of replication in macrophages. (See page 164).

Consequently, one of skill in the art would be forced into undue experimentation to determine which of the numerous genes, and more specifically which precise combination of inactivated genes within the SPI2 region would be required to be inactivated to produce a strain which is attenuated and non-reverting while retaining its ability to elicit an immune response. Given that Linde et al set forth that multiple gene disruptions are unpredictable, and that mutations with SPI2 regions do not necessarily result in attenuation, the skilled artisan would be required to preform excessive experimentation in a highly unpredictable field with limited guidance, to isolated the appropriate strain.

For reasons of record in Paper Number 13 as well as the reasons set forth above, this rejection is maintained.

2. The rejection of claim 5 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is maintained. This is a written description rejection.

Applicant's are asserting that the instant application is analogous to Example 14 of the Written Description Guidelines. In that Example the claim recites a protein having SEQ ID NO: 3 and variants thereof that are at least 95% identical to SEQ ID NO: 3 and catalyze the reaction of A to B. Applicant's assert that likewise, the functional inactivity is an impaired secretion system apparatus associated with the type III secretion system of Salmonella.

Applicant's arguments have been fully considered but are not found to be fully persuasive.

First, the example in the Written Description Guidelines clearly identifies a function which can be readily identified (e.g., enzyme catalyst). More importantly, the recitation of the activity appears in the claim. The instant application is distinct from Example 14, in that the instantly filed application does not identify a shared function. Simply reciting that the protein does **not** have a particular function, does not identify the members of the genus, since the number of proteins which do not display a particular function are virtually limitless.

Finally, the claims do not recite any level of activity or abolished activity. Consequently, the claims do not identify or distinguish members of the genus so that one of skill in the art can identify the members.

Claim 5 recites a polynucleotide segment which has 95% sequence identity to SEQ ID NO: 1.

The specification and claims do not indicate what distinguishing attributes are shared by the members of the genus. Thus, the scope of the claims includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, SEQ ID NO: 1 alone is insufficient to describe the genus. Thus, Applicant's have not described a function which is shared by SEQ ID NO: 1 which would adequately describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genus.

Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The protein itself is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016.

Applicants are directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1 "Written Description" Requirement, Federal Register, Vol. 64, No. 244, pages 71427-71440, Tuesday December 21, 1999.

For reasons of record in Paper Number 13 as well as the reasons set forth above, this rejection is maintained.

3. The rejection of claim 5 under 35 U.S.C. 112, second paragraph, as being vague and indefinite in the recitation of "stringent conditions." is maintained.

Applicant's have amended the claim to recite "hybridization in 50% formamide with washing at 65°C." However, the claims remain vague and indefinite.

Applicant's assert that the "washing step" is preformed at 65°C, however this is only half of the equation for determining what will hybridize to the claimed sequence. What are the chemical conditions involved? Without a clear definition as to both the chemical and physical conditions involved, one of skill in the art would be unable to determine the metes and bounds of the claimed invention.

For reasons of record in Paper Number 13 as well as the reasons set forth above, this rejection is maintained.

Claim Rejections - 35 USC § 102

4. The rejection of claims 1, 3-4, 8, 10, and 12-13 under 35 U.S.C. 102(b) as being anticipated by Holden is withdrawn in view of Applicant's assertions.

The following new grounds of rejection are applied to the amended claims:

Claim Rejections - 35 USC § 112

5. Claim 5 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Applicant's have amended claim 5 to recite "stringent hybridization conditions comprise hybridization in 50% formamide with washing at 65°C." Applicant's point to support in Shea et al (PNAS USA Vol. 93, pp 2593-2597, March 1996), specifically Figure 4. However, Figure 4 of Shea et al do not recite any specific stringent conditions. Consequently, Applicant is required to demonstrate clear support for the newly filed claim limitation (page and line number) or cancel the newly filed limitations.

Applicant's specification is also objected to as containing new matter for the same reasons. Applicant is required to demonstrate clear support for the newly added material in the specification or cancel the newly added material from the specification.

Claims 6-7 and 9 are objected to as depending upon a rejected base claim, however claims 6-7 and 9 are free of the prior art of record.

6. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Navarro, whose telephone number is (703) 306-3225. The examiner can be reached on Monday - Thursday from 8:00 AM - 6:00 PM. The examiner can be reached on alternate Fridays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Lynette Smith can be reached at (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Group 1645 by facsimile transmission. Papers should by faxed to Group 1645 via the PTO Fax Center located in Crystal

Mall 1. The faxing of such papers must conform with the notice published in the official Gazette 1096 OG 30 (November 15, 1989). The CMI Fax Center number is (703) 308-4242.

Mark Navarro

Primary Examiner

April 3, 2003